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Glycosylation with glycosyl benzyl phthalates as a new type of glycosyl donor†

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A glucopyranosyl benzyl phthalate, two mannopyranosyl benzyl phthalates, and a 2-deoxyglucopyranosyl benzyl phthalate, which were prepared from the corresponding 1-hydroxy sugars and benzyl hydrogen phthalate, were found to be efficient glycosyl donors in the glycosylations of various glycosyl acceptors using TMSOTf as a promoter.

Introduction

Development of efficient and stereoselective glycosylation methodologies has been one of the major concerns in synthetic organic chemistry in recent years due to important biological functions of complex oligosaccharides and glycoconjugates.[1–3] Devising new glycosyl donors and developing new activation systems for existing donors have led to major advances in this field. In this respect, there still remains a need for more efficient and generally applicable new glycosyl donors although quite efficient glycosyl donors are presently available.[4,5] In fact, there have been recent reports on new glycosyl donors and new activation systems.[6–13] We have also recently reported a novel type of glycosyl donor, the 2′-carboxybenzyl (CB) glycoside **A**, as shown in Fig. 1 for stereoselective β-mannopyranosylation[14] and 2-deoxyglycosylation[15] and applied this methodology to the synthesis of a tetrasaccharide.[16] Lactonization of the glycosyl triflate **B**, which was derived from the CB glycoside **A**, was the driving force for the facile generation of the oxocarbenium **C** for the glycosylation. In continuation of the search for more efficient glycosyl donors, we envisaged that treatment of the glycosyl benzyl phthalate **D** with Lewis acids would also generate the oxocarbenium ion **C** by cyclic anhydride formation as shown in Fig. 1. An added impetus to design the phthalate **D** comes from the fact that the method for the preparation of **D** could be useful complement to that for the preparation of **A**. The CB glycoside **A** was prepared from the glycosyl halide and thus the original anomeric oxygen atom was replaced by 2-(hydroxymethyl)benzoic acid such as in the case of preparation of thioglycosides[17] while, alternatively, the glycosyl benzyl phthalate **D** or the glycosyl hydrogen phthalate **E**‡ would be prepared from the 1-hydroxy sugar through retention of the anomeric oxygen atom such as in the case of the preparation of glycosyl trichloroacetimidates.[18] Herein we report the synthesis and glycosylation with the glycosyl benzyl phthalate **D** as a novel type of glycosyl donor.

Results and discussion

Crystalline benzyl hydrogen phthalate (**1**) was readily obtained in large quantities by the reaction of inexpensive phthalic anhydride and benzyl alcohol.[19] Esterification reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucose and compound **1** using DCC in the presence of a catalytic amount of DMAP provided glucopyranosyl benzyl phthalate **2** (α/β = 3 : 2) as shown in Scheme 1. Three more glycosyl benzyl phthalates, namely, tetra-*O*-benzyl-α-mannopyranosyl benzyl phthalate **3**,[20] 2-*O*-acetyltri-*O*-benzyl-α-mannopyranosyl benzyl phthalate **4**, and 2-deoxyglucopyranosyl benzyl phthalate

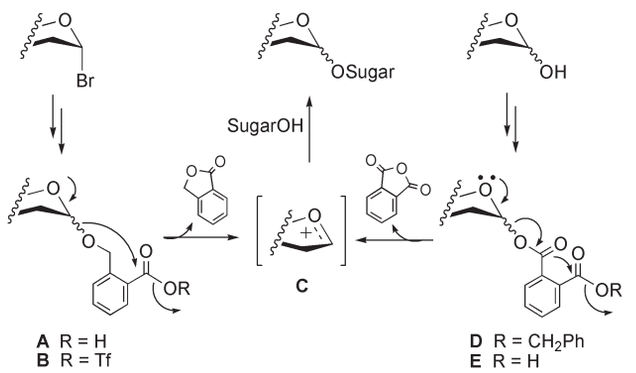
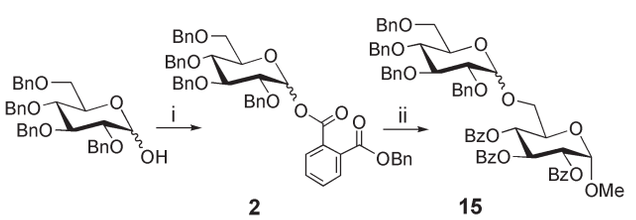
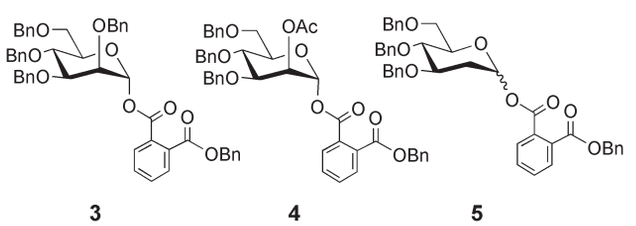


Fig. 1

5 (α/β = 1 : 1) were prepared from the corresponding 1-hydroxy sugars in analogous fashions. These glycosyl benzyl phthalates were stable enough to store at room temperature for a few months without any change.



Scheme 1 Reagents and conditions: i, benzyl hydrogen phthalate (**1**), DCC, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 3 h, 86% (α/β = 3 : 2); ii, **6**, TMSOTf, CH_2Cl_2, 0 °C, 1 h, 91% (α/β = 2.4 : 1).



Glucopyranosyl donor **2** was readily activated by TMSOTf in dichloromethane and coupled with various glycosyl acceptors to afford disaccharides in high to moderate yields. For instance, a solution of 1.0 equiv. of compound **2**, 2.0 equiv. of the primary alcohol acceptor **6**, and 0.5 equiv. of TMSOTf in dichloromethane was stirred at 0 °C for 1 h. After quenching with saturated aqueous sodium bicarbonate solution, the reaction mixture was purified by column chromatography to afford a mixture of α- and β-disaccharides **15** (α/β = 2.4 : 1) in 91% yield (Scheme 1 and entry 1 in Table 1). The glycosylation also proceeded with less than 0.5 equiv. of TMSOTf although more slowly. Reaction of compound **2** with other primary alcohol acceptors **7** and **8** similarly provided disaccharides **16** (α/β = 1.4 : 1) in 90% yield and **17** (α/β = 1.2 : 1) in 87% yield, respectively (entries 2 and 3 in Table 1). Coupling of donor **2** with secondary alcohol acceptors required a larger quantity of TMSOTf (1.0 equiv.) and a longer reaction time (1.5 h) and afforded β-disaccharides as

† Electronic supplementary information (ESI) available: Spectroscopic and analytical data for all new compounds. See http://www.rsc.org/suppdata/ob/b4/b405793g/

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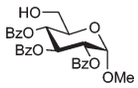
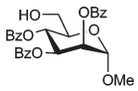
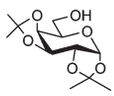
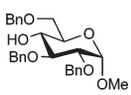
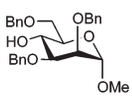
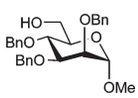
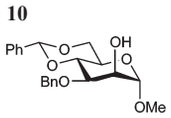
Table 1 Glycosylation with glycosyl benzyl phthalates **2**, **3**, and **4**[a]

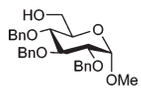
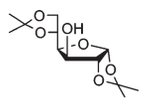
Entry	Donor	Acceptor	Product	Yield (%)[b]	Ratio (α/β)
1	**2**	 **6**	**15**	91	2.4 : 1
2	**2**	 **7**	**16**	90	1.4 : 1
3	**2**	 **8**	**17**	87	1.2 : 1
4	**2**	 **9**	**18**	63	1 : 5.5
5	**2**	 **10**	**19**	66	1 : 1.5
6	**3**	**6**	**20**	89	4 : 1
7	**3**	**7**	**21**	82	25 : 1
8	**3**	**8**	**22**	85	2.6 : 1
9	**3**	 **11**	**23**	75	3 : 2
10	**3**	**9**	**24**	73	α only
11	**3**	**10**	**25**	68	α only
12	**3**	 **12**	**26**	62	α only
13	**4**	**7**	**27**	76	α only
14	**4**	**9**	**28**	77	α only

[a] Glycosylation was carried out with 1.0 equiv.. of donor, 1.7 equiv.. of acceptor and TMSOTf (0.5 equiv.. for primary alcohol acceptors, 1.0 equiv.. for secondary alcohol acceptors) in dichloromethane at 0 °C for 1 h (for primary alcohol acceptors) or 1.5 h (for secondary alcohol acceptors). [b] Isolated yield.

major products but in a little lower yield than with primary alcohol acceptors. Thus, the reaction of 1.0 equiv. of glycosyl donor **2** with 2.0 equiv. of secondary alcohol acceptors **9** and **10** in the presence of 1.0 equiv. of TMSOTf in dichloromethane at 0 °C for 1.5 h gave disaccharides **18** in 63% yield and **19** in 66% yield, respectively (entries 4 and 5 in Table 1).

Reactions of tetra-*O*-benzylmannopyranosyl benzyl phthalate **3** with various glycosyl acceptors were also carried out under the same reaction condition as that with glucopyranosyl donor **2** and afforded disaccharides in reasonable yields. Unlike the glucopyranosyl donor **2**, the mannopyranosyl donor **3** exhibited α-selectivity regardless of primary or secondary alcohol acceptors and the selectivity was also more pronounced than that with **2**. Moderate (α/β = 2.6 : 1) to high (α/β = 25 : 1) α-selectivity was observed in the reaction of **3** with primary alcohol acceptors (entries 6–9 in Table 1) while α-disaccharides **24**, **25**,[21] and **26** were obtained exclusively in the reactions of **3** with secondary alcohol acceptors **9**, **10**, and **12**, respectively (entries 10–12 in Table 1). Coupling of 2-*O*-acetyl-tri-*O*-benzylmannosyl donor **4** with the primary alcohol acceptor **7** and with the secondary alcohol acceptor **9** afforded exclusively α-disaccharides **27** in 76% and **28** in 77% yields, respectively (entries 13 and 14 in Table 1). This result indicates that the neighboring group participation by the acetate at the C-2 position is operative in the present glycosylation using glycosyl benzyl phthalates.

Table 2 Glycosylation with the 2-deoxyglycosyl benzyl phthalate **5**[a]

Entry	Donor	Acceptor	Product	Yield (%)[b]	Ratio (α/β)
1	**5**	**6**	**29**	94	3 : 1
2	**5**	**7**	**30**	79	1.3 : 1
3	**5**	 **13**	**31**	89	1 : 1.2
4	**5**	**10**	**32**	78	α only
5	**5**	**12**	**33**	88	α only
6	**5**	 **14**	**34**	88	α only

[a] Glycosylation was carried out with 1.0 equiv.. of donor, 2.0 equiv.. of acceptor and 0.5 equiv.. of TMSOTf in dichloromethane at −78 °C to −40 °C. [b] Isolated yield.

2-Deoxyglucosyl benzyl phthalate **5** was found to be more reactive than glycosyl benzyl phthalates **2**, **3**, and **4** and could be activated by TMSOTf even at −78 °C to give a little higher yield of disaccharides. For example, to a solution of donor **5** (1.0 equiv.) and acceptor **6** (2.0 equiv.) in dichloromethane was added TMSOTf (0.5 equiv.) at −78 °C. The further reaction at −78 °C for 30 min and warming the reaction mixture over 1 h to −40 °C afforded disaccharide **29** (α/β = 3 : 1) in 94% yield (entry 1 in Table 2). Reaction of **5** with other primary alcohols **7** and **13** also gave a mixture of α- and β-disaccharides **30** (α/β = 1.3 : 1) in 79% yield and **31** (α/β = 1 : 1.2) in 89% yield, respectively (entries 2 and 3 in Table 2). Couplings of **5** with secondary alcohol acceptors **10**, **12**, and **14**, on the other hand, were completely stereoselective and afforded exclusively α-disaccharides **32**, **33**, and **34**, respectively in high yields (entry 4–6 in Table 2).

In conclusion, we have found that glycosyl benzyl phthalates behave as efficient glycosyl donors by extrusion of stable phthalic anhydride upon treatment with TMSOTf to afford disaccharides in the glycosylation of various glycosyl acceptors. Reactions of mannopyranosyl benzyl phthalate **3** and 2-deoxyglucopyranosyl benzyl phthalate **5**, which both have no participating group at C-2, with secondary alcohol acceptors were completely stereoselective to afford exclusively α-disaccharides.

Acknowledgements

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Notes and references

‡ The glycosyl hydrogen phthalate **E** was readily prepared by the reaction of 1-hydroxy sugar with phthalic anhydride in the presence of triethylamine but was found not to be a practical donor because of its partial decomposition during isolation and glycosylation.

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20 Typical procedure for the preparation of glycosyl benzyl phthalate **3**. To a solution of the 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (3.00 g, 5.4 mmol, 1.0 equiv.), benzyl hydrogen phthalate (**1**) (2.77 g, 10.8 mmol, 2.0 equiv.), and DMAP (200 mg, 1.64 mmol, 0.3 equiv.) in CH_2Cl_2 (20 mL) was added DCC (1.90 g, 9.2 mmol, 1.7 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, diluted with CH_2Cl_2 (50 mL), and filtered through Celite. The filtrate was washed with water, the combined organic layer was dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography to afford mannosyl benzyl phthalate **3** (3.36 g, 80%): R_f = 0.5 (*n*-hexane/EtOAc/CH_2Cl_2, 6 : 1 : 0.5, v/v); $[\alpha]_D^{20}$ = +29.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.72 (dd, $J_{5,6a}$ 1.6, $J_{6a,6b}$11.0 Hz, 1 H, H-6_a), 3.81 (dd, $J_{5,6b}$ 4.2, $J_{6a,6b}$ 11.0 Hz, 1 H, H-6_b), 3.88–3.95 (m, 2 H, H-2, H-3), 4.03–4.06 (m, 1 H, H-5), 4.14 (dd, $J_{3,4}$ 9.6, $J_{4,5}$ 9.6 Hz, 1 H, H-4), 4.53 and 4.67 (ABq, J_{AB} 12.1 Hz, 2 H, PhCH_2O), 4.54 and 4.90 (ABq, J_{AB} 10.6 Hz, 2 H, PhCH_2O), 4.57 (s, 2 H), 4.77 and 4.83 (ABq, J_{AB} 12.3 Hz, 2 H, PhCH_2O), 5.22 and 5.28 (ABq, J_{AB} 12.4 Hz, 2 H, PhCH_2O), 6.46 (d, $J_{1,2}$ 1.8 Hz, 1 H, H-1), 7.13–7.79 (m, 29 H, Ar*H*); ^{13}C NMR (63 MHz, $CDCl_3$) δ 67.6, 68.9, 71.9, 72.7, 73.3, 73.5, 74.2, 74.8, 75.4, 79.4, 93.7 (C-1), 127.6, 127.7, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.4, 128.6, 128.9, 129.3, 131.2, 131.3, 131.6, 132.1, 135.4, 138.0, 138.3, 138.3, 138.4, 166.0 (C=O), 166.8 (C=O).; Anal. Calcd for $C_{49}H_{46}O_9$: C, 75.56; H, 5.95. Found: C, 75.59; H, 6.03.
21 Typical procedure for the synthesis of disaccharide **25** by glycosylation with glycosyl benzyl phthalate **3**. A solution of the mannopyranosyl donor **3** (62 mg, 0.08 mmol, 1.0 equiv.), the acceptor **10** (74 mg, 0.16 mmol, 2.0 equiv.), and TMSOTf (14.5 µL, 1.0 equiv..) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 1.5 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (2 mL) and then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography to afford the disaccharide **25** (54 mg, 68%): colorless oil, R_f = 0.35 (*n*-hexane/EtOAc, 3;1, v/v); $[\alpha]_D^{20}$ = +14.2 (*c* = 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.37 (s, 3 H, CH_3O), 3.52 (d, *J* = 10.6 Hz, 1 H), 3.65 (dd, *J* = 4.22, 10.7 Hz, 1 H), 3.71–3.77 (m, 6 H), 3.81 (d, *J* = 8.5 Hz, 1 H), 3.83 (d, *J* = 9.3 Hz, 1 H), 3.98 (dd, *J* = 9.5, 9.5 Hz, 1 H), 4.06 (dd, *J* = 9.0, 9.0 Hz, 1 H), 4.25 (br s, 2 H), 4.34 (d, *J* = 11.6 Hz, 1 H), 4.42 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 10.9 Hz, 1 H), 4.50 (d, *J* = 10.8 Hz, 1 H), 4.51–4.56 (m, 3 H), 4.57 (d, *J* = 11.3 Hz, 1 H), 4.61 (d, *J* = 12.2 Hz, 1 H), 4.62 (d, *J* = 12.6 Hz, 1 H), 4.66 (d, *J* = 12.5 Hz, 1 H), 4.79 (br s, 1H, H-1′), 4.83 (d, *J* = 10.8 Hz, 1 H), 5.32 (br s, 1H, H-1), 7.17–7.31 (m, 35 H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.1, 69.3, 70.3, 71.2, 71.4, 72.0(2), 72.5, 73.0, 73.3, 73.5, 73.7, 74.8(2), 75.1, 75.9, 80.1, 80.3, 98.7 (C-1′), 100.1 (C-1), 127.2, 127.3, 127.6, 127.6, 127.8, 128.1, 128.4, 128.6, 138.3, 138.6, 138.7, 138.9.; Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.44; H, 6.78.